--28. (Amended) An oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase having a sequence as set forth in (SEQ ID NO:18), wherein:

(a) the oligonucleotide hybridizes with the ribonucleic acid under conditions of high stringency and is between 10 and 40 nucleotides in length;

(b) the internucleoside linkages of the oligonucleotide comprise at least one phosphorothioate linkage; and

(c) hybridization of the oligonucleotide to the ribonucleic acid inhibits expression of the heparanase.--

A5

A marked up copy of the amendments to the claims is attached hereto as **Exhibit A**.

REMARKS

Claims 1-28 are pending and under examination in the subject application. By this Amendment, applicants have canceled claim 8, and amended claims 1, 7, 9, 20, and 28. Applicants maintain that the amendments to the claims raise no issue of new matter. Support for the amendments to claim 1 may be found in the specification as originally filed at, *inter alia*, page 2, line 12 to page 3, line 25; and at page 12, lines 25 to 27. Claim 7 has merely been amended to correct an inadvertent typographical error. Support for the amendments to claim 9 may be found in the specification as originally filed at, *inter alia*, page 19, lines 1 to 6. Support for the amendments to claim 20 may be found in the specification as originally filed at page 20, lines 8-11 and

Exhibit B which provides the manufacturer-supplied chemical formulation of the product referred to as LIPOFECTIN in the application. Support for the amendments to claim 28 may be found in the specification as originally filed at, *inter alia*, page 12, lines 25 to 27. Accordingly, applicants request entry of this Amendment. After entry of this Amendment, claims 1-7 and 9-28 will be pending and under examination.

In the August 27, 2002 Office Action, the Examiner stated that claims 8 and 9 are objected to under 37 C.F.R. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner stated that applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The Examiner stated that claim 8 is drawn to the oligo of claim 1 that comprises a modified internucleoside linkage. The Examiner stated that however, the oligo of claim 1 already possesses a phosphorothioate linkage, which is a modified internucleoside linkage. The Examiner stated that thus, claim 8 is restating a limitation that already exists in claim 1. The Examiner stated that claim 9 ostensibly limits claim 8 to one of four types of modified internucleoside linkages; however, one of the listed species is a phosphodiester linkage, which is the native linkage of oligonucleotides, and thus not a modification as stipulated in claim 8. The Examiner stated that claim 9 effectively removes a limitation of claim 1.

In response, in order to expedite prosecution, but without conceding the correctness of the Examiner's position, applicants have canceled claim 8 and amended claim 9 to limit claim 1 in proper format.

The Examiner stated that claim 7 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated that said claim recites "the oligonucleotide of claim 1, wherein the sequence of the oligonucleotide is selected from the following:" and then lists three sequences that are separated by the conjunction "and". The Examiner stated that such use of the term "and" leaves the claims unclear as to whether one, two or all three will be selected. The Examiner stated that if only one is intended to be selected, the sequences should be separated by the term "or". The Examiner stated that if applicant intends otherwise, clarification is required to reflect the scope of the claim.

In response, in order to expedite prosecution, but without conceding the correctness of the Examiner's position, applicants have amended claim 7 to replace "and" with "or".

The Examiner stated that claim 20 contains the trademark/trade name LIPOFECTIN. The Examiner stated that where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. §112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The Examiner stated that the claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. The Examiner stated that a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. The Examiner stated that in the present case, the trademark/trade name is used to identify/describe a cationic nucleotide carrier and, accordingly,

the identification/description is indefinite.

In response, in order to expedite prosecution, but without conceding the correctness of the Examiner's position, applicants have amended claim 20 to refer to the manufacturer-supplied chemical formulation of LIPOFECTIN as shown in **Exhibit B.**

Accordingly, applicant respectfully requests that the Examiner withdraw the objections to the claims in light of the arguments presented hereinabove.

Claims Rejected Under 35 U.S.C. §112

The Examiner stated that claims 1-6, 8 and 10-28 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner stated that applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001).

The Examiner stated that claim 1 of the above inventions is drawn to any "oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase". The Examiner stated that the specification provides a description of a heparanase polynucleotide isoform that comprises the target, represented by SEQ ID NO:17. The Examiner stated that however, the specification goes on to define all references to heparanase as encompassing all heparanase variants, natural or otherwise, that may be within 80% similarity of said heparanase, wherein said similarity may include conservative nucleotide substitutions

so long as heparanase function is retained. The Examiner stated that additionally, the language of claim 1 broadly contemplates sequences complementary to any heparanase. The Examiner stated that the specification as filed does not appear to disclose any additional species of heparanase other than that disclosed at SEQ ID NO:17, and that since the language of claim 1 clearly encompasses all antisense oligonucleotides that may be complementary to a heparanase, the person of ordinary skill in the art would need to be able to determine from the present specification a representative number of polynucleotide sequences of heparanase that might comprise such targets, in order to determine the suitable complements of each heparanase sequence and thus practice the invention as claimed.

The Examiner stated that in order to envision the genus of such heparanase targets, the specification should include a representative sample from heparanase of all species that express said protein, all isoforms, all alleles present within each of these species, and finally all variants that are within 80% similarity of said protein that retain heparanase function. The Examiner stated that a person of skill in the art would not view SEQ ID NO:17 of the specification as being representative of the broad genus of all heparanases claimed, and would thus conclude that applicant was not in possession of the invention as broadly contemplated. The Examiner stated that moreover, without a specific description of additional sequences or specific domains or motifs having the requisite heparanase activity, the skilled artisan would not readily envision any other target beyond SEQ ID NO:17. The Examiner stated that the specification thus provides description for SEQ ID NO:1, but not for sequences that are antisense to any polynucleotide encoding heparanase that are heretofore undescribed.

The Examiner stated that claims 15, 16, and 21-27 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of heparanase expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of heparanase expression *in vivo* (whole animals) or for methods of treating diseases associated with its expression *in vivo*. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Examiner stated that the above invention is drawn to methods of inhibiting the expression of heparanase in a cell, which may be a cancer cell, comprising contacting said cell with antisense compositions that inhibit the expression of heparanase. The Examiner stated that the claims of the above invention are also drawn to methods of treating a subject having a condition associated with heparanase, wherein said compositions are administered to animals such that expression of heparanase is inhibited, wherein said condition may be cancer, which may be characterized by tumor metastasis, or involves reduction of angiogenesis, wherein the language of said claims encompasses *in vivo* activity. The Examiner stated that the specification teaches a method of using the claimed compositions to inhibit the expression of heparanase in T24 bladder carcinoma cell line.

The Examiner stated that the specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds or methods of using said compounds in *in vivo* environments. The Examiner stated that additionally, a person skilled in the art would recognize that

predicting the efficacy of an antisense compound *in vivo* based solely on its performance *in vitro* is highly problematic. The Examiner stated that thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable.

The Examiner stated that a recent (2002) article by Braasch et al. opens by emphasizing that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology". The Examiner stated that "many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). The Examiner stated that Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo:* poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

The Examiner stated that regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). The Examiner stated that Branch adds that "internal structures of target RNAs and their associations with cellular proteins create

physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). The Examiner stated that additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target (Page 3161, second and third columns).

The Examiner stated that the uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "oligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides". The Examiner stated that cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. The Examiner stated that it is, therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378), and that "microinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379).

The Examiner stated that Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce

artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). The Examiner stated that Branch (1998) affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, these effects must be explored on case by case basis" (Page 50), while Tamm et al. states that "immune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has be ascertained experimentally" (page 493, right column). The Examiner stated that, further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is know, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). The Examiner stated that Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The Examiner stated that the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the in vivo treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above. The Examiner stated that furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of heparanase expression *in vitro* as being correlative or representative of the successful *in vivo* use of antisense

compounds or treatment of any and/or all conditions or diseases suspected of being associated with heparanase expression. The Examiner stated that this is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The Examiner stated that the specification as filed fails to provide any particular guidance which resolves the unknown unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

The Examiner stated that said claims are drawn very broadly to compounds and methods of treating or preventing any condition or disease suspected of being associated with heparanase expression in humans. The Examiner stated that the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with low toxicity and immunogenicity that are successfully delivered, and most importantly, that target sites in appropriate cells and/or tissue harboring heparanase expression such that all harmful expression is inhibited, that healthy expression is permitted appropriately *in vivo*, and further, that treatment and/or preventive effects are provided for any/or all diseases or conditions suspected of being associated with heparanase expression *in vivo*. The Examiner stated that since the specification fails to provide any guidance for the successful treatment or prevention of any and/or all diseases or conditions suspected of being associated with heparanase expression in humans, or their tissues or cells, and since resolution of the

various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation as presented in the specification over the scope claimed.

In response, applicants maintain that the specification reasonably conveys to one of skill in the art that the inventors had possession of the claimed invention. In particular, claims 1 and 28 as amended recite SEQ ID NO:18, specifically pointing out the heparanase sequence. With regard to claims 15, 16, and 21-27, applicants initially note that M.P.E.P. 2164.03 states that only a "reasonable correlation between the disclosed in vitro utility and an in vivo activity" is required for enablement.

In addition, applicants note that the examiner must give reasons for a conclusion of lack of correlation for an in vitro example (M.P.E.P. §2164.03). The Examiner cites Braasch et al. (2002), stating that "internal structures of target RNAs .... create physical barriers rendering most sites inaccessible to antisense molecules". Applicants have demonstrated heparanase antisense efficacy *in situ* - i.e. inside intact cells where the physical barriers mentioned by Braasch et al. already exist (see specification at page 23, line 19 to page 24, line 23). In addition, the antisense molecules claimed by applicants are clearly taken up by the cells as their exemplified efficacy demonstrates, and Agrawal as cited by the Examiner takes no position that such delivery does not work *in vivo*. Moreover, the Examiner has not stated why an antisense oligonucleotide would have to be taken up with the same efficiency by different cell types in order to be active in those cells. Indeed, Agrawal

teaches that antisense oligonucleotides can inhibit disease-associated proteins, and that their specificity and application has been verified in animal models of disease (see Abstract). Furthermore, Tamm et al. cited by the Examiner, teaches proven therapeutic use of antisense oligonucleotides, approved by the FDA (see page 490 of reference).

The Examiner also refers to non-specific toxicity effects of *in vivo* antisense administration. However, applicants note that, in general, all useful drug therapies have side effects (i.e. toxicity), and in particular note that anti-cancer drugs having high toxicity are routinely used in cancer therapy (see Tamm et al., p489, first paragraph). Toxicity does not preclude activity or usefulness. Furthermore, applicants note that it is well within the ordinary skill of one in the art to perform routine dosage determination (which is sufficient for enablement, see M.P.E.P. §2164.01(c)). Applicants also note that the therapeutic activity of the claimed oligonucleotides is defined by their sequence - the scrambled sequences do not work (see specification, page 24, lines 13 to 18).

As noted hereinabove, there need only be a reasonable correlation between *in vitro* activity and therapeutic utility. Applicants note Examiner has not cited reasons as to why the heparanase antisense oligonucleotides would not be expected to have useful activity *in vivo*, and note that reasonable correlation exists based on the specification itself as pointed out hereinabove, and other examples of *in vitro* and *in vivo* correlation, e.g. see Uchida et al. attached hereto as **Exhibit C**.

Applicants also note that the Examiner implies that the claimed invention requires the limitations of low toxicity, low

immunogenicity and complete lack of harmful heparanase expression for patentability. Applicants further note that M.P.E.P. §2107.02 states that "office personnel should ... not read into a claim unclaimed results, limitations or embodiments". Applicants assert that these unreasonably rigorous limitations imposed by the Examiner are not required for usefulness, activity, or patentability.

Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the rejection to the claims under 35 U.S.C. §112, first paragraph, in light of the arguments presented hereinabove.

Claims rejected under 35 U.S.C. §102(b)

The Examiner stated that 1-6, 8-12, 14, 17-19, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Graham et al., WO 96/08559. The Examiner stated that the claims of the above invention are drawn to an oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase, wherein said oligo is 10-40 nucleotides long, contains at least one phosphorothioate linkage, inhibits at least 50% as measured by western blot, wherein said oligo is made of DNA or RNA, or wherein said oligo is composed of 100% phosphorothioate linkages, or wherein said oligo is 15-25 nucleotides long, or is 20 nucleotides long, or comprises a internucleoside, sugar, or base modifications, or wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide inhibits expression of heparanase.

The Examiner stated that Graham et al. teach oligonucleotides that have a sequence complementary to a ribonucleic acid encoding a heparanase, wherein said oligo is 10-40 nucleotides long, contains at least one phosphorothioate linkage, and fully inhibits expression, wherein said oligo is made of DNA or RNA, or wherein said oligo is composed of 100% phosphorothioate linkages, wherein said oligo is about 20 nucleotides and comprises internucleoside, sugar, and base modifications, wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide inhibits expression of heparanase. The Examiner stated that applicant's inclusion of a Western blot protocol as they assay of choice to verify inhibition of heparanase expression in claim 1 is a design choice that doesn't influence the patentability of the oligonucleotide itself, and has not been treated as materially important in the present examination.

In response, applicants note that, contrary to the Examiner's assertion, Graham et al. does no teach "oligonucleotides that have a sequence complementary to a ribonucleic acid encoding a heparanase". In fact, Graham et al. teach that sequence complementarity is unimportant for the non-complementary GT-rich oligonucleotides they disclose, see for example page 16, lines 17 to 20. Indeed, Graham et al. do not refer to any oligonucleotides that have a sequence complementary to a ribonucleic acid encoding a heparanase. Moreover, Graham et al. does not teach an oligonucleotide having a sequence complementary to a heparanase having a sequence as set forth in SEQ ID NO:18, as recited in amended claims 1 and 28. Accordingly, Graham et al. fails to teach an essential element of applicants' claimed invention.

The Examiner also stated that claims 1-3, 5, 6, 14, 17-19, and 28 are rejected under 35 U.S.C. §102(e) as being anticipated by Pecker et al. (WO 00/52178). The Examiner stated that the claims of the above invention are drawn to an oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase, wherein said oligo is at least 10 to 40 nucleotides long, may contain at least one phosphorothioate linkage, inhibits heparanase expression at least 50% as measured by Western blot, wherein said oligo is made of DNA or RNA, or is made of 15-25, or about 20 nucleotides, or wherein said target is human heparanase, or wherein said oligo is an a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide can be used for the formation of pharmaceutical compounds, or inhibits expression of human heparanase.

The Examiner stated that the claims of the above invention are drawn to an oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding acid encoding a heparanase, wherein said oligo is at least 10 nucleotides long, may contain at least one phosphorothioate linkage, inhibits heparanase expression, wherein said oligo is made of DNA or RNA, or may comprise internucleoside, sugar, or base modifications, or wherein said target is human heparanase, or wherein said oligo is in a composition comprising a carrier, wherein said carrier can pass through a cell wall, or is cationic, or wherein the oligonucleotide inhibits expression of heparanase.

In response, applicants note that Pecker at al. does not teach an oligonucleotide having a sequence complementary to SEQ ID NO:18, as recited in amended claims 1 and 28. In fact, Pecker et

al. does not teach any heparanase antisense oligonucleotide sequences. In addition, and in contrast to applicant's claimed invention, Pecker et al. does not teach the sub-genus of oligonucleotides directed to heparanase which inhibit heparanase expression. Although the Examiner has stated that applicants' inclusion of a Western blot protocol to verify inhibition of heparanase expression in claim 1 is a design choice that doesn't influence the patentability of the oligonucleotide itself, applicants maintain that verifying heparanase inhibition is an essential element of the invention. As is acknowledged in the field, acknowledged in the references cited by Examiner (see Braasch et al., Introduction), and exemplified in the present application (see for example page 25, line 28 to page 26, line 14; and page 23, line 20 to page 24, line 18), it is not possible to predict whether a given antisense sequence will act to inhibit expression of the protein, and this must be verified experimentally. Pecker et al. discloses oligonucleotides directed to a heparanase, whereas applicants claim a sub-genus of active oligonucleotides that inhibit heparanase expression.

Accordingly, applicant's maintain that Pecker et al. does not teach applicants' claimed invention, and applicants request that the Examiner reconsider and withdraw the rejection of the claims.

Claims rejected under 35 U.S.C. §103

The Examiner stated that the claims 1, 12, and 13 are rejected under 35 U.S.C. §103(a) as being unpatentable over Graham et al., in view of Froehler et al. (U.S. Patent No. 5,484,908). The Examiner stated that claim 13 of the instant application is directed to the antisense oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a

heparanase, wherein said oligo is at least 10 to 40 nucleotides long, contains at least one phosphorothioate linkage, wherein said oligo inhibits heparanase expression, wherein the nucleobase is modified to comprise 5-methyl pyrimidine or 5-propynyl pyrimidine. The Examiner stated that Graham et al. teaches antisense oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase, wherein said oligo is at least 10 to 40 nucleotides long, contains at least one phosphorothioate linkage, wherein said oligo inhibits heparanase expression, and teaches nucleobases modifications to said oligo, but does not teach 5-methyl pyrimidine or 5-propynyl pyrimidine modifications. The Examiner stated that Froehler et al. teaches 5-propynyl pyrimidine modifications of oligo nucleobases.

The Examiner stated that it would have been obvious for one of ordinary skill in the art to take the heparanase antisense oligos as taught by Graham et al. and incorporate 5-propynyl pyrimidine modifications into them as taught by Froehler et al. The Examiner stated that once one would have been motivated to do so because Froehler et al. teach that such modifications enhance binding of the antisense oligo to the target gene, which is the key step in antisense oligo-mediated inhibition. The Examiner stated that one of ordinary skill in the art would have had a reasonable expectation of success in doing so, because Froehler et al. provide detailed instructions on its synthesis, and because such modifications are routinely performed by those of ordinary skill in the art. The Examiner stated thus, in the absence of evidence to the contrary, the invention of claim 13 would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was filed.

In response, applicants note that, contrary to the Examiner's assertion, Graham et al. in combination with Froehler et al. do not teach "oligonucleotides that have a sequence complementary to a ribonucleic acid encoding a heparanase". In fact, Graham et al. in combination with Froehler et al. teach that sequence complementarity is unimportant for the GT rich oligonucleotides they exemplify, for example see page 16, lines 17 to 20 of Graham et al. Indeed, Graham et al. does not refer to any oligonucleotides that have a sequence complementary to a ribonucleic acid encoding a heparanase. Moreover, Graham et al. in combination with Froehler et al. do not teach an oligonucleotide having a sequence complementary to SEQ ID NO:18, as recited in amended claims 1 and 28. Thus, Graham et al. in combination with Froehler et al. fail to teach elements of applicants' claimed invention.

Accordingly, applicants maintain that the Examiner has not set forth a case of prima facie obviousness over the cited references, and thus, claims 1, 12, and 13 satisfy the requirements of 35 U.S.C. §103.

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. § 1.56, applicants direct the Examiner's attention to the following references which are listed on the attached Form PTO-1449 (**Exhibit D**) and attached hereto as **Exhibits 1-2:**

1. WO96/08559 A1, Cardiac CRC Nominees Pty. Ltd, published March 21, 1996 (Exhibit 1); and

2. WO 00/52178 A1, Insight Strategy & Marketing, Ltd.,

published September 8, 2000 (Exhibit 2).

References 1-2 were first cited in an International Search Report issued in connection with counterpart application PCT/US02/20636 **Exhibit 3**).

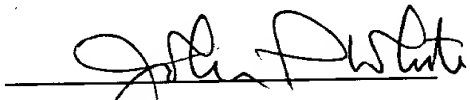
This Second Supplemental Information Disclosure Statement supplements the Information Disclosure Statement filed March 4, 2002 and the Supplemental Information Disclosure Statement filed June 25, 2002 by applicants in connection with the above-identified application.

This Supplemental Information Disclosure Statement is submitted under 37 C.F.R. §1.97(c). Accordingly, the undersigned hereby certifies pursuant to 37 C.F.R. §1.97(e) that each item of information contained in this Second Supplemental Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Second Supplemental Information Disclosure Statement

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $55.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Amendment. If any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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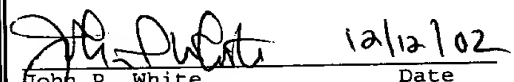
I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.



12/12/02
John P. White Date
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Marked-Up Copy of Amendments to the Claims

Claims 1, 7, 8, 9, 20, and 28 have been amended as follows:

--1. An oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase having a sequence as set forth in (SEQ ID NO:18), wherein:

(a) the oligonucleotide hybridizes with the ribonucleic acid under conditions of high stringency and is between 10 and 40 nucleotides in length;

(b) the internucleoside linkages of the oligonucleotide comprise at least one phosphorothioate linkage; and

(c) hybridization of the oligonucleotide to the ribonucleic acid inhibits expression of the heparanase, wherein inhibition of heparanase expression means at least a 50% reduction in the quantity of heparanase as follows: (a) a T24 bladder carcinoma cell is exposed to a complex of the oligonucleotide and lipofectin at an oligonucleotide concentration of 1 μM and a lipofectin concentration of 10 μg/ml for 5 hours at 37°C, (b) the complex is completely removed after such exposure, (c) 19 hours later the cell is scraped, washed and extracted in lysis buffer, (d) the nucleus of the cell is removed by centrifugation, (e) the cytoplasmic proteins in the resulting supernatant are separated according to mass by sodium dodecyl sulphate polyacrylamide gel electrophoresis, (f) the protein is transferred to a polyvinylidene difluoride membrane that is incubated at room temperature for 1-2 hours in incubation solution (g) the membrane is exposed to

1 μg/ml of an antibody directed against heparanase at 4°C for 12 hours, (h) the membrane is exposed to wash buffer and incubated for 1 hour at room temperature in blocking buffer comprising a 1:3,000 dilution of a peroxidase-conjugated secondary antibody directed against an epitope on the antibody directed against heparanase, (i) the membrane is exposed to a chemiluminescent cyclic diacylthydrazide and the oxidation of the cyclic diacylthydrazide by the peroxidase is detected as a chemiluminescent signal, and (j) the signal is quantitated by laser-scanning densitometry as a measure of the amount of heparanase expressed calculated as a percentage of heparanase expression in an untreated cell.--

--7. (Amended) The oligonucleotide of claim 1, wherein the sequence of the oligonucleotide is selected from the following:

(a) CCCCAGGAGCAGCAGCAGCA (SEQ ID NO:3);

(b) GTCCAGGAGCAACTGAGCAT (SEQ ID NO:4); or [and]

(c) AGGTGGACTTTCTTAGAAGT (SEQ ID NO:5).

--9. (Amended) The oligonucleotide of claim [8] 1, further comprising [wherein the modified internucleoside linkage is] a peptide-nucleic acid linkage[,] or a morpholino linkage[, a phosphodiester linkage or a stereo-regular phosphorothioate].--

--20. (Amended) The composition of claim 19, wherein the cationic reagent is [lipofectin] a 1:1 (w/w) liposome formulation of a cationic lipid N-[1-(2,3-dioleyloxy)propyl]-N,N,N-trimethylammonium chloride and

dioleoyl phosphatidylethanolamine.--

--28. (Amended) An oligonucleotide having a sequence complementary to a sequence of a ribonucleic acid encoding a heparanase having a sequence as set forth in (SEQ ID NO:18), wherein:

(a) the oligonucleotide hybridizes with the ribonucleic acid under conditions of high stringency and is between 10 and 40 nucleotides in length;

(b) the internucleoside linkages of the oligonucleotide comprise at least one phosphorothioate linkage; and

(c) hybridization of the oligonucleotide to the ribonucleic acid inhibits expression of the heparanase.